Remarks/Arguments

Claims 1-8 and 19-24 were examined in this case. Claims 1-8 and 19-24 stand rejected. Each of the objections and rejections raised in the Office Action is addressed individually below.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-8 and 19-24 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. The Examiner asserts that the instant disclosure does not place any limits on genera listed in the claims, including "unstructured nucleic acid(s)" which are "substantially complementary" to a first template sequence element, as well as "purine analog(s)" and "pyrimidine analog(s)".

Regarding the claim term "unstructured nucleic acids(s)", Applicant notes that an identical written description rejection was already levied by the previous Examiner, and that Applicant successfully overcame this rejection by identifying relevant passages from the specification that defined this term. See pages 3-4 of the Office Action issued May 23, 2001 and pages 8-9 of the Response filed October 16, 2001 (reprinted below in pertinent part).

> The Examiner asserts that the claims are drawn to methods of making "unstructured" nucleic acids, but the term "unstructured" is unclear since all nucleic acids have some structure. In response, Applicant points out that the term "unstructured nucleic acids" is defined in the specification. The specification states that
>
> > "nucleic acid molecules having reduced levels of secondary structure compared to nucleic acid molecules of the same nucleotide sequence containing only naturally-occurring bases. . . are referred to herein as "unstructured nucleic acids" (UNAs). UNAs have reduced levels of secondary structure because of their reduced ability to form intramolecular hydrogen bond base pairs between regions of substantially complementary sequence. Preferred UNAs, however, retain the ability to form intermolecular hydrogen bond base pairs with other nucleic acid molecules" (page 15, lines 2-10).
>
> The specification further describes what is meant by "unstructured nucleic acids" by stating that

> "UNAs contain nucleotide base analogs or a mixture of base analogs and naturally-occurring bases such that regions of sequence complementarity within the UNA are unable to form base pairs. One or both of the nucleotides that together form an intramolecular complementary base pair are substituted with a nucleotide containing a base analog so that the base pair is no longer formed, or is only formed at a reduced level. Preferably, the reduced level of base pairing is no more than one hydrogen bond interaction. Preferably, the analog(s) is selected so that the UNAs retain the ability to hybridize with another nucleic acid molecule of complementary or substantially complementary sequence" (page 15, lines 11-18).

As but one last example, Applicant points to page 22, lines 20-22, which state that

> "UNAs are produced such that sequence elements in the UNA have a reduced ability to hybridize to substantially complementary sequence elements within the same UNA polynucleotide molecule."

Indeed, the specification proceeds to describe the particular base pairing concepts of unstructured nucleic acids in detail at page 15, line 19 to page 17, line 3.

> In light of the definition of unstructured nucleic acids provided in the specification, this aspect of the rejection should be withdrawn.

Regarding the claim term "substantially complementary", Applicant points out that this term is also clearly defined in the specification. The specification states that, "For purposes of the present invention, two sequence elements are considered substantially complementary if at least 50% of the nucleotides in the two elements can form stable hydrogen bonds. Preferably, sequence elements are considered substantially complementary if at least 75% of the nucleotides can form stable hydrogen bonded base pairs. More preferably, sequence elements are considered substantially complementary if at least 85% of the nucleotides can form stable hydrogen bonded base pairs. Most preferably, sequence elements are considered substantially complementary if at least 95% of the nucleotides can form stable hydrogen bonded base pairs" (page 12, lines 2-9).

The Examiner's rejection of the claim terms "purine analog(s)" and "pyrimidine analog(s)" is rendered moot in light of the current amendments to the pending claims.

In light of the clear definitions provided in the specification for "unstructured nucleic acid(s)" and "substantially complementary", one skilled in the art would undoubtedly understand that Applicant had possession of the invention as claimed.

Double Patenting

Claims 1-8 and 19-24 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of copending Application No. 09/632,639. Applicant respectfully refrains from commenting on the present provisional obviousness-type double patenting rejection until such time as Applicant is notified that the provisional rejection has matured into an actual rejection.

Rejection Under 35 U.S.C. §102(e)

Claims 1-8 and 19-24 stand rejected as being unpatentable under 35 U.S.C. §102(e) as being anticipated by Vivekananda et al. (U.S. Patent No. 6,569,630) and Kutyavin et al. (U.S. Patent No. 5,912,340). The Examiner asserts that the two references teach methods comprising synthesizing nucleic acid molecules with a reduction or alteration in secondary structure through the utilization of nucleotides recited in the currently pending claims. Applicant respectfully submits that neither reference anticipates the currently pending claims.

Contrary to the Examiner's assertion, Vivekananda et al. do not teach methods of synthesizing nucleic acid molecules with reduced secondary structure. Vivekananda et al. disclose a method of detecting anthrax spores and other chemical and biological agents. They achieve this by utilizing nucleic acid molecules that are able to specifically bind particular targets, preferably through non-Watson-Crick interactions. Specifically, Vivekananda et al. define their preferred nucleic acid aptamers as "a nucleic acid that binds to another molecule ('target' as defined below). This binding interaction does not encompass standard nucleic acid/nucleic acid hydrogen bond formation exemplified by Watson-Crick basepair formation (e.g., A binds to U or T and G binds to C), but encompasses all other types of non-covalent (or in some cases covalent) binding" (column 8, lines 27-33). The intended binding target of Vivekananda et al.'s nucleic acids are "any compound or aggregate of interest. Non-limiting examples include a protein, peptide, carbohydrate, polysaccharide, glycoprotein, lipid, hormone, receptor, antigen, allergen, antibody, substrate, metabolite, cofactor, inhibitor, drug,

pharmaceutical, nutrient, toxin, cholera toxin, Shiga-like toxin, poison, explosive, pesticide, chemical warfare agent, biohazardous agent, prion, radioisotope, vitamin, heterocyclic aromatic compound, carcinogen, mutagen, narcotic, amphetamine, barbiturate, hallucinogen, waste product, contaminant or other molecule" (column 8, lines 46-56). Thus, the Vivekanada et al. nucleic acids are not designed to bind to other nucleic acids, at least not through Watson-Crick-type interactions.

By contrast, the present claims are directed to methods of producing a nucleic acid that *forms intermolecular interactions with a complementary nucleic strand,* but has reduced ability to form intramolecular basepairs. Currently amended claim 1 recites a method of synthesizing an unstructured nucleic acid by "providing a nucleic acid template strand including a first template sequence element and a second template sequence element that is substantially complementary to the first template sequence element" and "providing a collection of nucleotides including at least a first complementary nucleotide *that hybridizes with a first residue within the first sequence element on the template strand* and a second complementary nucleotide *that hybridizes with a second residue within the second sequence element on the template strand*, wherein... the first and second nucleotides have a reduced ability to form a stable hydrogen bonded base pair." Vivekananda et al. simply do not teach or suggest such a method, and thus cannot anticipate the present claims.

Kutyavin et al. disclose a matched set of oligonucleotides containing modified nucleotides such that each member of the matched set is able to hybridize with a complementary strand in a duplex nucleic acid molecule, but is unable to hybridize with the other member of the matched set. A key limitation cited throughout the Kutyavin et al. disclosure is that there must be a matched set of oligonucleotides that are unable to hybridize with each other. In contrast, currently amended claim 1 recites a single unstructured nucleic acid that contains nucleotides having "a reduced ability to form an intramolecular base pair." Although Kutyavin et al. do describe an embodiment wherein the matched set of oligonucleotides are covalently linked to one another via "tethers", they specifically state that such a tether should be selected such that it does not participate in hybridization with complementary sequences in the duplex nucleic acid molecule (col. 9, lines 38-45). Thus Kutyavin et al. explicitly teach away from the present invention wherein the entire unstructured nucleic acid recited in the present claims hybridizes with a complementary strand in the duplex nucleic acid molecule.

Since there is no teaching or suggestion that their method can be used to construct a single unstructured nucleic acid that has a reduced ability to form intramolecular base pairs, Kutyavin et al. cannot anticipate the currently pending claims.